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| EXAMINER | |
|---|---|
| QAZI, SABIHA NAIM | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/509,074 | CHEN ET AL. | |
| | Examiner | Art Unit | |
| | Sabiha Qazi | 1612 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11/13/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *21-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**Final Office Action**

Claims 21-26 are pending. New claims are added. Amendments are entered. No claim is allowed. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

**Summary of this Office Action dated 2/11/2009**

1. 35 USC § 112 (2) Rejection
2. 35 USC § 112 (1) Rejection
3. 35 USC § 103(a) Rejection
4. Response to Remarks
5. Conclusion
6. Communication

## Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 21 and 26 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claim 21 is incomplete. Definitions of substituents are missing.

4. Claim 26 improperly depends on claims 1 or 2. There is no claim 1 or 2.

## Claims Claim Rejections - 35 USC § 112 – First Paragraph Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-26 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melonama by compound 0058 (JS-38) in the specification,

does not reasonable provide enablement for the **treating or preventing proliferative** diseases in a human or an animal comprising administration to the human or animal of a therapeutic amount of a compound of the formula wherein Z = aryl, heterocylic, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl group, while X and Y can be the same or different, are hydrogen, substituted or unsubstituted alkyl, cycloalkyl, aryl, aralkyl or heterocyclic group.

Amended claim 22 contains specific compounds, contains large number of combination of substituents having different substituents at X, Y and Z. for example Z can be morpholine, piperazine, thiophene, pyridinium, pyrrole, imidazole. Specification does not contain any data or guidance for the treatment and "prevention" of proliferative disease.
Furthermore, there is no guidance or teaching how and when human or an animal will be prevented.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the

enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

**The nature of the invention:** The claims are drawn to a method of treating or preventing proliferative diseases in a human or an animal comprising administration to the human or animal of a therapeutic amount of a compound of the formula as in claim 21, wherein Z, X and Y can have variety of substituents containing heterocyclic and non-heterocyclic groups. Each has different chemical structure and expected to have different properties.

**The predictability or unpredictability of the art:** There is lack of

predictability in the in the pharmaceutical art especially in the methods for treatment or prevention of proliferative disease.

Evidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to a method of treating seven types of cancer with members of a class of several compounds. In re Buting, 163 USPQ 689. The disclosure provides no indication of whether the compounds treat all cancers. To make clearer the lack of enablement for treatment of all cancer, extrinsic evidence is supplied by DRAETTA (Ann. Reports Med. Chem.), DRAETTA et al. in "Annual Reports in Medicinal Chemistry"., 1996, Academic Press, San Diego, pp 241-246, final sentence on page 246 although many still think about the need for a magic bullet as a cure for all cancers, our knowledge of the molecular mechanism underlying this disease make the prospect of developing such a universal cure very unlikely." Since no universal cure for cancer has been developed, it follows that there is no correlation between the assays relied upon by applicants and the ability for the treatment and prophylaxis of proliferative diseases as has been claimed in claim 19. Thus, those assays are not sufficient to enable such claims.

Further, in the art of clinical oncology, no compound has yet shown clinical efficacy against every type of cancer. Different agents are used for different forms

of cancer and no single agent is listed as a treatment of every single type of cancer. BALASUBRAMANIAN reference (Recent Developments in Cancer Cytotoxics) on page 151 first paragraph "the successful treatment of solid tumors remains a formidable challenge."

Applicant has provided no evidence, which incontrovertibly demonstrates that the tests set forth in the instant specification are art-recognized, reliable predictors of successful treatable, in vivo, of all cancers. The worker of ordinary skill in the art would not be able to practice the instantly claimed method, since no description is found of an actual method wherein a cancer in a host is treated. Applicants fail to fulfill the requirement of 35 U.S.C. 112, first paragraph, by failing to provide an adequate written description of how to treat all cancers in a single host.

**The Breadth of the claims**

Since the instant specification provides no limiting definition of the term "prevention", the term will be interpreted expansively. The term "prevention" may vary widely in meaning, from "preventing" a disease from occurring to "preventing" it from progressing. Nor is the term limited by any time frame.

The claims are thus very broad insofar as they suggest that one will not experience the disease when taking the claimed agent; that should one get the

disease, it will not worsen; or that following its treatment, it will not recur. While such "prevention" might theoretically be possible under strictly controlled laboratory conditions, as a practical matter it is nearly impossible to achieve in the "real world" in which patients live.

**The amount of direction or guidance presented:** There is no guidance in the disclosure on how to use the invention successfully for the treatment or prophylaxis of ***any*** proliferative diseases as claimed. There is one compound 0058 (JS-38) which has been tested. The inventor provides very little direction in the instant specification. Only limited substitutents on the compounds arernade and disclosed. There are no compounds R2 and R3 forming a ring, The availability of the starting material that is needed to prepare the invention as claimed is also at issue here. As per MPEP 2164.01 (b): A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. The Court in In re Ghiron, 442 F.2d 985,991,169 USPQ 723,727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a

chemical process. In re Howarth, 654 F.2d 103, 105,210 USPQ 689, 691 (CCPA 1981). There is no guidance for the starting material provided with respect to the various substituents.

The instant specification does not have any working examples with respect to the various substituents as given above. The state of the art indicates that even when the reactants are similar, and the reaction conditions are the same, it is not necessary that it would form the same products.

In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result."

The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "...

where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971).

**The presence or absence of working examples:** A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

**The quantity of experimentation necessary:** Since there is no guidance presented in the disclosure, how to treat or prevent "proliferative diseases" successfully by claimed compounds, one skilled in the art at the time of invention would have to go through undue experimentation to make and/or use the presently claimed invention.

***Claim Rejections - 35 USC § 103***

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21-26 rejected under 35 U.S.C. 103(a) as being unpatentable over WEBSTER et al.[1] and GODFREY[2]. Both the references teach dithiolopyrrolones and their derivatives as presently claimed.

WEBSTER teaches dithiolpyrroles as antineoplastic agents. See the entire document especially abstract, figure 1 on page 1, figures 2 and 3 on page 2, examples and claims.

GODFREY teaches these compounds as fungicides. See the entire document especially compounds of formula (1) on page 1, Table 1 on page 3continued to page 5scheme 1 on page 7examples and claims.

Instant claims are generically taught by the prior art.

Instant claims differ from the reference in that they are of different generic scope. It had been held by Courts that the indiscriminate selection of "some" from among "many" is considered prima facie obvious. In re Lemin, 141 USPQ 814 (1964); National Distillers and Chem. Corp. V. Brenner, 156 USPQ 163.

The instant claimed compounds would have been obvious because one skilled in the art would have been motivated to prepare compounds embraced by the genus of the above cited references with the expectation of obtaining additional

[1] WO 99/12543
[2] GB 2,173,499

beneficial compounds. The instant claimed compounds would have been suggested to one skilled in the art.

One having ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within the genus. In re Susi, 440 F.2d 442, 445, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in Merck & Co. V. Biocraft Laboratories, 874 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

In the light of the forgoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the instant claims would have obvious to one skilled in the art.

**Response to Remarks**

Applicants' arguments have been fully considered but were not found persuasive. Claim 19 rejected under 35 U.S.C. 101 are withdrawn because claim is cancelled.

**Conclusion**

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**.

See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

**Communication**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sabiha Qazi whose telephone number is (571) 272-0622. The examiner can normally be reached on any business day except Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sabiha Qazi/
Primary Examiner, Art Unit 1612